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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,852	09/09/2003	Jeroen Demmer	11000.1070U	3215

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/657,852	DEMMER ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1-5,10-25,28,30-33 and 35* is/are withdrawn from consideration.

5)☒ Claim(s) *6-8* is/are allowed.

6)☒ Claim(s) *9,26,27,29,34 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 09/16/05 has been acknowledged.
The sequence listing filed on 09/16/05 has been acknowledged.

Election/Restrictions

Earlier applicant's elected without traverse of Group II claims 6-9, 26-27, 29 and 34, wherein the elected subject matter is SEQ ID NO:15 (encoded by SEQ ID NO:3) in the reply filed on 02/22/05.

This application contains claims 1-5, 10-25, 28, 30-33 and 35 drawn to an invention nonelected with traverse in Paper No. 02/22/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Claim Rejections - 35 USC § 112

Claims 9, 26-27, 29, 34 and 36-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the office action mailed on 05/07/05.

The scope of invention as claimed encompasses any and all variants of SEQ ID NO:15 having lat least 90% to 98% identity (2-10% variation) to the amino acid sequences of SEQ ID NO:15. At best the specification discloses the SEQ ID NO: 15, which encodes an antifreeze protein (AFP2). However, the

specification fails to disclose any other natural or non-natural variant of SEQ ID NO:15 that has an ability to bind ice crystals.

Applicant is referred to the guidelines for *Written Description Requirement* published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In instant case the specification discloses the SEQ ID NO: 15, which encodes an antifreeze protein.

In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification does not provide the structure of any other variant of SEQ ID NO:15 that has the asserted functional activity. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The specification fails to disclose any other variant of SEQ ID NO:15 having any other relevant identifying characteristics. It is not possible to envision the claimed compositions because it is not known what are the different variants of this protein and what particulars mutations, such as point mutations, deletion mutations or any other sequence changes would be present. Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

Furthermore, the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).*

In the instant case the variants (as claimed) has been defined only by a statement of function that broadly encompasses an ability to bind ice crystals-like activity, which conveyed no distinguishing information about the identity of the claimed amino acid sequence, such as its relevant structural or physical characteristics. In instant case the variation as claimed also encompasses the conserved motifs, which are considered germane to the functional activity of an antifreeze-like polypeptide. Furthermore 2-10% variation (90-98% identical) as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. In addition, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Response to arguments

Regarding written description issue the applicant arguments filed on pages 7-8 of response filed on 09/16/05 has been fully considered. The applicant argues that claim 9 has been amended to limit the variants of SEQ ID NO:15 having al least 90-98% sequence identity. The applicant argues that claim 9 does not encompass polypeptides having sequence variations in the conserved motifs found in the antifreeze proteins that would render the polypeptide unable to bind to ice crystals, as the claim clearly requires that the polypeptides possess this functional activity. The applicant argues that the invention as claimed meets written descritption guidelines as the polypeptide as claimed possess sufficient common identifying characteristics, namely specific percentages of sequence identity and clearly recited functional characteristics, to clearly distinguish the clâimed polypeptides from other materials and that these identifying characteristics would indeed lead one of skill in the art to conclude that the applicant was in possession of the claimed invention at the time the application was filed.

However, applicant's arguments are found not persuasive because the invention as claimed herein is not limited to any variant of SEQ ID NO:15 where there is no variation in the region that comprises motifs germane for the antifreeze activity. As stated earlier the variants (as claimed) has been defined only by a statement of function that broadly encompasses an ability of the claimed polypeptide variant to bind ice crystals, which conveyed no distinguishing information about the identity of the claimed amino acid sequence, such as its relevant structural or physical characteristics. Besides the nucleotide sequences of SEQ ID NO:15 the specification as filed fails to disclose any variant of SEQ NO:15 that has the claimed anti-freeze activity. In instant case the variation as claimed encompasses the conserved motifs, which are considered germane to the functional activity of an antifreeze-like polypeptide. Furthermore 2-10% variation would affect the protein folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 9, 26-27, 29, 34 and 36-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequences of SEQ ID NO:15, wherein the polypeptide is encoded by the nucleotide sequence of SEQ ID NO:3, does not reasonably provide enablement for any and all natural or non natural variants of SEQ ID NO:15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in

scope with these claims, for the same reasons of record as set forth in the office action mailed on 05/07/05.

Nature Of Invention:

The invention relates to an antifreeze protein.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses any and all variants of SEQ ID NO:15, wherein at least 2-10% (90%-98% identity) of amino acid sequences has been added, deleted or substituted over the entire length of SEQ ID NO:15.

State Of Art And Predictability:

The antifreeze proteins have evolved to meet the special task of protecting small water and land animals, as well as some plants, from freezing. Their special mode of interaction with the ice lattice suppresses the freezing point of water by up to several degrees. Freezing is a process of ice crystallization from super cooled water. Ice should first experience ice nucleation, followed by growth. Whether or not freezing takes place is determined to a large extent by ice nucleation. There is evidence that fish antifreeze proteins bind to and reduce the efficiency of heterogeneous nucleation sites, rather than binding to embryonic ice nuclei. The antifreeze action of the AFP is actually first to inhibit the nucleation by terminating the relevant kinetics (Strom et al. J Am Chem Soc. 127(1):428-440, 2005, Davies et al, Philos Trans R Soc Lond B Biol Sci. 357(1423):927-35, 2002). Furthermore the mechanisms by which the antifreeze protein (AFP) modifies the ice morphology is complex, since the growth morphology of the AFP-ice system is derived from various factors, including the face indices, surface molecular compositions, relative growth rates, and the mechanisms responsible for that morphology. Storm et al J Biol Chem. 279(31):32407-417. 2004).

The scope of invention as claimed encompasses variation in conserved amino acid sequence domain that is considered essential for an ability to bind ice crystals. This renders the invention as claimed unpredictable, since applicant wish to identify a variant that does not even comprises the conserved amino acid sequences required for antifreeze activity. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The variants as claimed are only hypothetical proteins because no biological function has been established. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston:

Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976).

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). In instant case screening of any and all natural and non-natural variants, wherein at least 2-10% of amino acid are added substituted and/or deleted in the disclosed SEQ ID NO:15 is not considered routine. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 2-10% amino acids are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed antifreeze activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. Therefore, the applicant has not presented enablement commensurate in scope with the claims.

Response to arguments

Regarding enablement issues the applicant arguments filed on pages 8-9 of response filed on 09/16/05 has been fully considered. The applicant argues that the claim 9 as amended is drawn to polypeptides comprising a sequence having at least 90-98% identity to SEQ ID NO: 15, wherein the polypeptide possesses an ability to bind ice crystals. The applicant argues that variants as claimed encompasses no change in conserved motifs, since the variants as claimed possess the ability to bind ice crystals. The applicant argues that level of skill in the field of biotechnology in generally higher, therefore screening variants is predictable and would not require undue amount of experimentation.

However, applicant's arguments are found not persuasive because as stated above the invention as claimed is not limited to a variant of SEQ ID NO:15 where there is no variation in the region that comprises motifs germane for the antifreeze activity. In

instant case the variants (as claimed) has been defined only by a statement of function that broadly encompasses an ability of the variant polypeptide to bind ice crystals, which conveyed no distinguishing information about the identity of the claimed amino acid sequence, such as its relevant structural or physical characteristics. Besides the amino acid sequences of SEQ ID NO:15 the specification fails to disclose any variant of SEQ ID NO:15 that has the asserted functional activity. The variation as claimed encompasses the conserved motifs, which are considered germane to the functional activity of an antifreeze-like polypeptide. Furthermore 2-10% variation would affect the protein folding and biological activity if amino acids that are critical for such functions are substituted, added or deleted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. In addition screening of any and all natural and non-natural variants, wherein at least 2-10% of amino acid are added substituted and/or deleted in the disclosed SEQ ID NO:15 is not considered routine. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 2-10% amino acids are added, deleted and/or substituted. For example making a polypeptide with at least 10% sequence variation would encompasses modification of at least 27 amino acid sequences over the entire length of SEQ ID NO:15 which is a 267 residue long protein. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed having the asserted functional activity. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed antifreeze activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Conclusion

Claims 6-8 are free of prior art of record. The prior art does not teach or suggest isolated polypeptide comprising the amino acid sequences of SEQ ID NO:15 encoded by the nucleic acid sequences of SEQ ID NO:3.

Claims 9, 26-27, 29, 34 and 36-39 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633